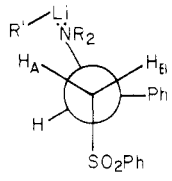

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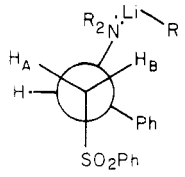

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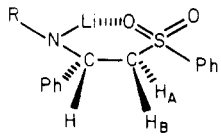

11

The *opposite* diastereoselectivity observed in the lithiation of the amino derivatives of **6** (R_2N = H_2N or MeHN) suggests that initially the amino proton is replaced by lithium and a rigid chelate involving coordination of the lithium center by both the RN^- and SO_2 groups, may be a reasonable intermediate for proton abstraction (**11**). An external base (RLi) or a base coordinated at nitrogen should be able to abstract H_B with a lower $\Delta G^{\ddagger}$ than that required for H_A because approach to the flank phenyl group is avoided (cf. footnote 8 for further mechanistic implications).

A typical procedure for preparing **6a** and then lithiating such a phenyl 2-amino-2-phenylethyl sulfone is as follows. A warm solution of phenyl (*E*)-β-styryl sulfone (**1c**, 12.2 g, 50 mmol) in 30 mL of 95% alcohol was sealed in a Hoke tube together with 16.87 g (0.15 mol) of a 40% aqueous dimethylamine solution. The tube was heated for 48 h on a steam bath, cooled, emptied, and rinsed with chloroform. The solvents were removed in vacuo and the residue was recrystallized from 95% ethanol to give 10.54 g (73%) of **6a**, mp 132–134 °C. In $CDCl_3$ the NMR spectrum showed δ 7.82 (m, 2), 7.53 (m, 3), 7.25 (m, 5) 4.28–3.28 (m, 3), and 2.0 (s, 6). In $CDCl_3$–CF_3CO_2H the NMR spectrum showed δ 7.60–6.83 (m, 10), 4.87 (m, 1), 4.17 (m, 2), 2.88 (d, 3, J = 4 Hz), and 2.70 (d, 3, J = 4 Hz). The addition of 5.5 mmol (3.44 mL of a 1.6 M solution in hexane) of *n*-butyllithium to a solution of 1.45 g (5.0 mmol) of **6a** in 40 mL of anhydrous THF cooled in a CO_2/acetone bath was followed after 15 min by the addition of 6.0 mmol of CH_3I. After 15 min more at −78 °C, the reaction was quenched with aqueous NH_4Cl. After the solution was warmed to 25 °C, usual workup gave 1.51 g (99%) of a colorless solid. The NMR spectrum indicated this product to be a 84:16 mixture of **7a** and **8a**. When this mixture was retreated with *n*-butyllithium in THF as above, stirred for 1 h in an ice bath, and quenched, workup as before showed a 55:45 mixture of **7a** and **8a**. Isomer **8a**, mp 158–60 °C, could be obtained by several recrystallizations of such mixtures from 95% EtOH. In $CDCl_3$ the NMR spectrum of **8a** showed δ 7.8–6.9 (m, 10), 4.1–3.68 (m, 2), 2.03 (s, 6), and 1.68 (imperfect t, 3, J = 7 Hz). In $CDCl_3/CF_3CO_2H$ the NMR spectrum of **8a** showed δ 7.70–7.05 (m, 10), 4.68–3.97 (m, 2), 3.10 (d, 3, J = 4 Hz), 2.74 (d, 3, J = 4 Hz), and 1.30 (d, 3, J = 6 Hz). Further processing of the above mother liquors gave **7a**, mp 112–114 °C (hexane). Isomer **7a** showed the following NMR spectrum: ($CDCl_3/CF_3CO_2H$) δ 8.0–7.0 (m, 10), 4.86 (d, 1, J = 11 Hz), 4.42–3.63 (m, 1), 2.97 (d, 3, J = 4 Hz), 2.85 (d, 3, J = 4 Hz), and 0.95 (d, 3, J = 6 Hz).

(8) This mechanistic proposal requires that the thermodynamic acidity of the CH_2SO_2 protons be greater than that of the RNH protons but that the kinetic acidity of the RNH protons be greater than that of the CH_2SO_2 protons. Both requirements can find support in previous work: (1) the pK_a values of $CH_3SO_2CH_3$ and $(CH_3CH_2)_2NH$ are 23 and 36, respectively; (2) cyclohexylamine and piperidine (or their lithium salts) are widely used kinetic bases for promoting the deprotonation of carbon acids. Cf. D. J. Cram, "Fundamentals of Carbanion Chemistry", Academic Press, New York, 1965, pp 15–16, 20–31; R. Huisgen and J. Sauer, *Angew. Chem.*, **72**, 91 (1960).

(9) All new compounds exhibited spectral and analytical properties in accord with the assigned structures.

Registry No. **1c**, 16212-06-9; **6a**, 65885-20-3; **6b**, 75032-53-0; **6c**, 75032-54-1; **6d**, 75032-55-2; **7a**, 75032-56-3; **7b**, 75032-57-4; **7c**, 75032-58-5; **8a**, 75032-59-6; **8b**, 75032-60-9; **8c**, 75032-61-0; **8d**, 75032-62-1; **9**, 72568-90-2.

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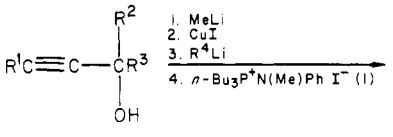
Organocuprate-Induced Coupling of Propargyl or Enyne Alcohols Using (Methylphenylamino)tributylphosphonium Iodide. Regiocontrolled Synthesis of Allenes and Conjugated Enynes

Summary: Regioselective synthesis of allenes is directly achieved via organocuprate-mediated γ-coupling of propargyl alcohols by using the title reagent (**1**). Alternatively, the coupling between 1,4-enyn-3-ols and alkyllithium affords the conjugated *Z* enynes regio- and stereoselectively.

Sir: Recently, interest in allenic chemistry has been noted from both mechanistic[1] and synthetic aspects,[2] and a number of synthetic methods for allenes have been hitherto published.[3] 1,3-Coupling (S_N2' reaction) between propargyl units and alkyl groups in diorganocuprates appears to be one of the most valuable methods for synthesis of allenes. However, besides requiring an excess of alkyl groups in the cuprate reagents, the previous processes require propargyl derivatives such as an ether,[3a] acetate,[3b] tosylate,[3c] halide,[3d] sulfinate,[3e] and carbamate,[3f] which are not always accessible.

We now communicate a highly regiocontrolled alkylation of propargyl or enyne alcohols via organocopper intermediates by using the reagent **1**,[4] which affords an efficient method for synthesis of allenes (eq 1) or conjugated enynes (eq 2).



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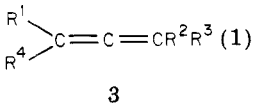

3

The full scope of the allene synthesis is summarized in Table I. This new synthetic method for allenes has proven to be valuable in the following aspects. (1) The reaction

(1) Claesson, A.; Olsson, L. I. *J. Am. Chem. Soc.* **1979**, *101*, 7302 and references cited therein.

(2) (a) Crabbé, P.; Carpio, H. *J. Chem. Soc., Chem. Commun.* **1972**, 904. (b) Crabbé, P.; Andre, D.; Fillion, H. *Tetrahedron Lett.* **1979**, 893. (c) Reich, H. J.; Olson, R. E.; Clark, M. C. *J. Am. Chem. Soc.* **1980**, *102*, 1423. For a review article concerning the enallene system, see: (d) Henrick, C. A. *Tetrahedron* **1977**, *33*, 1845.

(3) (a) Olsson, L. I.; Claesson, A. *Acta Chem. Scand., Ser. B* **1979**, 679. (b) Rona, P.; Crabbé, P. *J. Am. Chem. Soc.* **1969**, *91*, 3289. (c) Vermeer, P.; Meijer, J.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas* **1975**, *94*, 112. (d) Pasto, D. J.; Shults, R. H.; McGrath, J. A.; Waterhouse, A. *J. Org. Chem.* **1978**, *43*, 1389. (e) Kleijn, H.; Elsevier, C. J.; Westmijze, H.; Meijer, J.; Vermeer, P. *Tetrahedron Lett.* **1979**, 3101. (f) Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950.

(4) Tanigawa, Y.; Ohta, H.; Sonoda, A.; Murahashi, S.-I. *J. Am. Chem. Soc.* **1978**, *100*, 4610.

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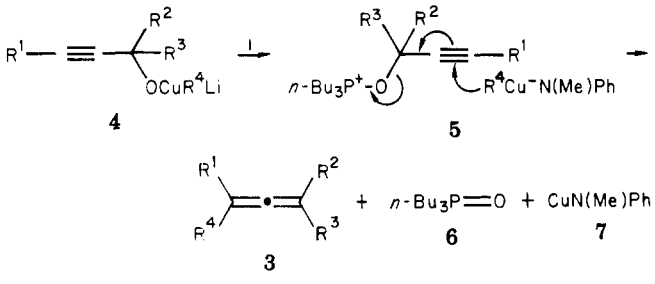
Table I. Alkylation and Arylation of Propargyl Alcohols[a]

entry	substrate 2 R¹	R²	R³	organolithium[b]	allene 3,[c] % yield[d,e]
1	Ph	H	H	MeLi	34[f,g]
2	Ph	Ph	H	MeLi	67
3	Ph	Et	H	MeLi	72
4	$PhSCH_2$	Et	H	*n*-BuLi	68
5	Me_3Si	*n*-Bu	H	MeLi	67
6	*n*-Bu	Ph	Me	MeLi	82
7	*n*-Bu	$-(CH_2)_5-$		PhLi	70

[a] All reactions were performed on a 3-5-mmol scale with the same procedure as described in the text. [b] 1 equiv of organolithium was used. [c] All products have been characterized by spectral means and elemental compositions. [d] All yields are based on isolated pure substances by preparative TLC on silica gel unless otherwise indicated. [e] In all reactions, starting alcohols 2 were recovered in 5–23%. [f] Isolated yield by reduced pressure distillation. [g] The residue was polymerized materials.

Scheme I

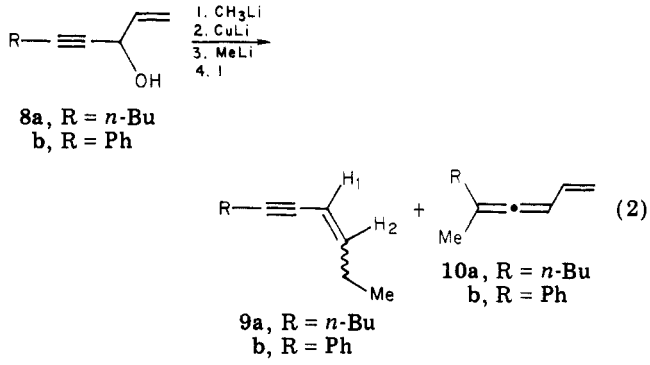


is quite general and substituted allenes are directly prepared from primary, secondary, and tertiary propargyl alcohols with complete regioselectivity (S_N2' reaction). (2) One need not employ any propargyl alcohol derivatives as starting materials or an excess of organolithium compounds. (3) Phenylthio or trimethylsilyl functionalized propargyl alcohols, which are readily available,[5] are converted into the corresponding allenes in good yields, thereby enhancing the synthetic utility of the reaction (entries 4 and 5).

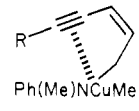
The course of the reaction can be rationalized by assuming Scheme I. Nucleophilic attack of the counterion, alkyl (methylphenylamino)cuprate, toward the γ-carbon of the propargyloxy group of the intermediate **5**, which is initially formed from **4** and **1**, would produce the desired allene **3** along with tributylphosphine oxide (**6**) and (methylphenylamino)copper (**7**).

Surprisingly, even in the case of the alcohol **2** (R^1 = Me_3Si; R^2 = *n*-Bu; R^3 = H) with a sterically bulky group at its terminal acetylene carbon, the alkylation smoothly proceeds to give the allene **3** with complete regioselectivity (entry 5).[6] Consequently, it suggests that the steric effect of the substituent on the substrate[7] does not exert any influence on the regioselectivity in our reaction systems. From consideration of our previous work[4] in which a highly regioselective γ-coupling between allyl units and alkyl groups is achieved by using **1**, the regioselectivity in the present reactions seems to be strongly dependent on the nature of the leaving group and the substituent on copper.[8]

These considerations prompted us to investigate the alkylation of enyne alcohols as depicted in eq 2. Interestingly, contrary to a general trend in coupling pattern,[9] which produces an enallene predominantly from an enyne acetate and diorganocuprate,[10] enyne alcohols **8** afforded the conjugated *Z* enynes **9** regio- and stereoselectively under the present reaction conditions.[11] Thus, non-1-en-4-yn-3-ol (**8a**) was methylated to produce the conjugated *Z* enyne **9a** (71%; *Z*/*E* = 96/4 by GLC)[12] along with the enallene **10a** (3%) in 74% total isolated yield. Furthermore, 1-phenylpent-4-en-1-yn-3-ol (**8b**)[12] gave the conjugated *Z* enyne **9b** (66%; *Z*/*E* = 80/20 by GLC) with **10b** (9%) in 75% total isolated yield.



Although the remarkable difference in reactivity patterns between these coupling reactions is still ambiguous, a key step in the sequence might be the formation of a highly reactive allylic copper(III) intermediate such as **11**.



11

The present methodology is undoubtedly one of the most attractive methods for the synthesis of allenes or conjugated enynes. The preparation of 2-phenylhexa-2,3-diene is representative (entry 3). To an orange suspension of the lithium (propargyloxy)(methyl)cuprate **4**, which is prepared from 1-phenylpent-1-yn-3-ol (3 mmol, 0.481 g), methyllithium in ether (1.85 M, 6.3 mmol), and cuprous iodide (3 mmol, 0.571 g) in dry THF (15 mL) at −70 °C, was added a solution of **1** (3 mmol, 1.306 g) in dry DMF (15 mL) at the same temperature under Ar. After the solution was stirred for 3 h at −70 °C to room temperature followed by treatment with 2 N HCl aqueous solution (20 mL), the solvent was removed in vacuo. Column chromatography followed by preparative TLC on silica gel gave the desired allene (0.33 g, 72% isolated yield; EtOAc–hexane (1:9), R_f 0.78) and the unreacted alcohol (0.11 g, 10%; EtOAc–hexane (1:9), R_f 0.20).[13]

(5) Brandsma, L. "Preparative Acetylenic Chemistry"; Elsevier: Amsterdam, 1971.
(6) GLC analysis showed no contamination with the isomeric acetylene, 1-(trimethylsilyl)-3-methylhept-1-yne.
(7) Brinkmeyer, S. R.; Macdonald, T. L. *J. Chem. Soc., Chem. Commun.* **1978**, 876.
(8) Alternative studies concerning these effects will be published elsewhere by Y. Tanigawa.
(9) (a) Descoins, C.; Henrick, C. A.; Siddall, J. B. *Tetrahedron Lett.* **1972**, 3777. For a related system, see: (b) Baudouv, R.; Delbecq, F.; Goré, J. *Ibid.* **1979**, 937.
(10) The reaction of 3-acetoxynon-1-en-4-yne (2 mmol) with lithium dimethylcuprate (2 mmol) in dry ether at −20 °C to room temperature for 2 h produced the conjugated *Z* enyne **9a** (15%, *Z*/*E* = 63/37 by GLC) along with the enallene **10a** (31%) in 46% total isolated yield (see ref 9a).[12]
(11) For a regio- and stereocontrolled synthesis of conjugated *Z* enynes induced by organocopper(I), see: (a) Cassani, G.; Massardo, P.; Piccardi, P. *Tetrahedron Lett.* **1979**, 633; (b) Kleijn, H.; Westmijze, H.; Kruithof, K.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 27.
(12) The stereochemistry of compounds **9** was characterized by the coupling constant of olefinic protons ($J_{H_1-H_2}$, Hz) in the ^1H NMR as follows: (*E*)-**9a**, 16; (*Z*)-**9a**, 11; (*E*)-**9b**, 16.5; (*Z*)-**9b**, 10.5.
(13) GLC analysis of the reaction mixture before column chromatography showed no detectable amounts of the isomeric acetylene, 1-phenyl-3-methylpent-1-yne.

Registry No. 1, 67660-23-5; 2 (R^1 = Ph; R^2 = R^3 = H), 1504-58-1; 2 (R^1 = Ph; R^2 = Ph; R^3 = H), 1817-49-8; 2 (R^1 = Ph; R^2 = Et; R^3 = H), 27975-78-6; 2 (R^1 = $PhSCH_2$; R^2 = Et; R^3 = H), 75031-46-8; 2 (R^1 = TMS; R^2 = Bu; R^3 = H), 75045-85-1; 2 (R^1 = Bu; R^2 = Ph; R^3 = Me), 18215-71-9; 2 (R^1 = Bu; R^2, R^3 = $-(CH_2)_5-$), 15332-33-9; 3 (R^1 = Ph; R^2 = R^3 = H; R^4 = Me), 22433-39-2; 3 (R^1 = Ph; R^2 = Ph; R^3 = H; R^4 = Me), 53544-89-1; 3 (R^1 = Ph; R^2 = Et; R^3 = H; R^4 = Me), 75031-47-9; 3 (R^1 = $PhSCH_2$; R^2 = Et; R^3 = H; R^4 = Bu), 75031-48-0; 3 (R^1 = TMS; R^2 = Bu; R^3 = H; R^4 = Me), 75031-49-1; 3 (R^1 = Bu; R^2 = Ph; R^3 = Me; R^4 = Me), 75031-50-4; 3 (R^1 = Bu; R^2, R^3 = $-(CH_2)_5-$; R^4 = Ph), 75031-51-5; **8a**, 67978-48-7; **8a** acetate, 75031-52-6; **8b**, 40964-63-4; (*E*)-**9a**, 56392-49-5; (*Z*)-**9a**, 56392-46-2; (*E*)-**9b**, 31552-03-1; (*Z*)-**9b**, 31552-04-2; **10a**, 59415-24-6; **10b**, 75031-53-7; CuI, 7681-65-4.

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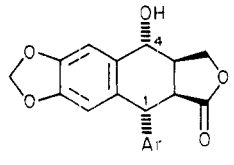
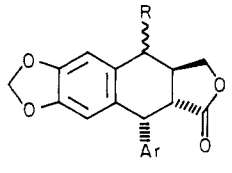
A Stereo- and Regiocontrolled Synthesis of Podophyllum Lignans

Summary: A Diels–Alder adduct of an isobenzofuran (generated in situ) and dimethyl acetylenedicarboxylate is converted by a series of controlled reductions and isomerizations to the lignans deoxy- and isodeoxypodophyllotoxin in seven stages.

Sir: The potent antimitotic activity of the *Podophyllum* lignans has been the subject of much chemical and biochemical study.[1] Structural and stereochemical parameters for the inhibition of tubulin polymerization by these compounds have been recently defined.[2] The pioneering synthetic efforts of Gensler et al. resulted[3] in a route to picropodophyllin (1) which was subsequently converted to its THP-enolate and kinetically reprotonated to podophyllotoxin (2). Subsequently, two other formal syntheses



1



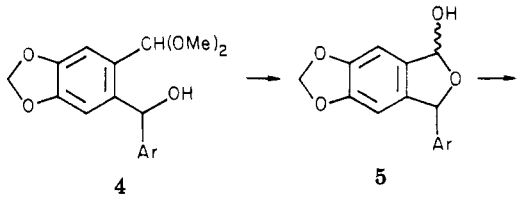
2, R = α-OH
3, R = H

Ar = 3,4,5-trimethoxyphenyl

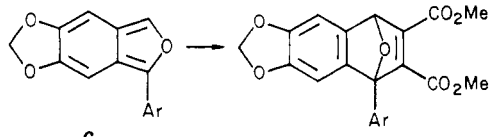
have been reported,[4] each relying ultimately on the enolate reprotonation as before. No other successful synthetic strategy has yet been demonstrated for the elaboration of the strained 1,2-*cis*,2,3-*trans* system of these compounds. This stereochemistry which is crucial to the antimitotic activity of these compounds is also the major obstacle in the way of a simple synthesis of these relatively simple molecules.

We now describe an eight-step solution to the problem and illustrate it herein with the total synthesis of the antimitotic lignan (±)-deoxypodophyllotoxin (3). In order to circumvent the problem of facile epimerization of the *cis*-1-phenyltetralin *trans*-2,3-lactones, we have selected a suitable bicyclo precursor, established the necessary 1,2,3 stereo- and regiochemistry and then generated the desired phenyltetralin system under nonbasic conditions.

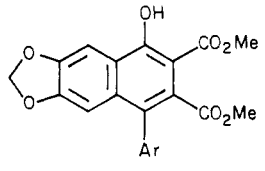
The dimethyl acetal of 6-bromopiperonal was lithiated and reacted with 3,4,5-trimethoxybenzaldehyde as before[5,6] to yield the crystalline alcohol 4. This compound upon brief treatment on a steam bath with excess dimethyl acetylenedicarboxylate and a catalytic quantity of glacial acetic acid was converted through intermediates 5 and 6 to the crystalline oxygen-bridged Diels–Alder adduct 7.[7]



4 5



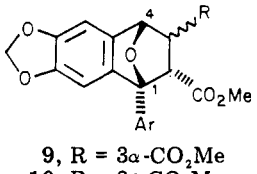
6 7



8

Ar = 3,4,5-trimethoxyphenyl

The mother liquors contained the hemiacetal 5 which was recycled without isolation in the same manner. The recycling procedure is essential, since any attempt to effect a complete conversion of 4 to 7 in one pass results in the production of substantial quantities of the isomeric naphthol 8. In this manner an overall yield of 67% was achieved. The realization of 7 in satisfactory yield was our first important goal. It provided in two steps the required carbon atoms and is our bicyclo substrate upon which a series of carefully chosen regio- and stereocontrolled transformations were carried out. Hydrogenation (H_2, Pd, ethyl acetate, 50 psi), resulted in the quantitative and exclusive formation of the endo ester 9. The stereochemical outcome of the hydrogenation was immediately



9, R = 3α-CO_2Me
10, R = 3β-CO_2Me
11, R = 3β-CH_2OH

Ar = 3,4,5-trimethoxyphenyl

(1) For reviews, see: Hartwell, J. L.; Schrecker, A. W. *Fortschr. Chem. Naturst.* **1958**, *15*, 83; Ayres, D. C. In "Chemistry of Lignans"; Rao, C. B. S., Ed.; Andhra University Press: India, 1978.
(2) Brewer, C. F.; Loike, J. D.; Horowitz, S. B.; Sternlicht, H.; Gensler, W. J. *J. Med. Chem.* **1979**, *22*, 215; *Cancer Res.* **1978**, *38*, 2688. Kelleher, J. K. *Cancer Treat. Rep.* **1978**, *62*, 1443.
(3) Gensler, W. J.; Gatsonis, C. D. *J. Org. Chem.* **1966**, *31*, 4004.
(4) Kende, A. S.; Liebeskind, L. S.; Mills, J. E.; Rutledge, P. S.; Curran, D. P. *J. Am. Chem. Soc.* **1977**, *99*, 6082. Murphy, W. S.; Wattanasin, S. *J. Chem. Soc., Chem. Commun.* **1980**, 262.
(5) Plaumann, H. P.; Smith, J. G.; Rodrigo, R. *J. Chem. Soc., Chem. Commun.* **1980**, 354.
(6) ^{1}H NMR spectra were determined in $CDCl_3$ at 60, 80, 220, and 360 MHz as required. Instruments operating in the FT mode were used at the last three frequencies. Melting points were determined on a Büchi SMP-20 unit and are uncorrected. Acceptable elemental analyses were obtained for all new compounds.
(7) 7: mp 159 °C; ^{1}H NMR δ 3.73 (s, 3 H), 3.77 (s, 3 H), 3.87 (s, 9 H), 5.90 (close q, 2 H), 5.95 (s, 1 H), 6.77 (s, 2 H), 6.90 (s, 2 H); IR ($CHCl_3$) $\nu_{C=O}$ 1720 cm^{-1}.

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